Exhibit 13

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Pressure Ulcer Research

Current and Future Perspectives

Springer

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technologist or radiologist performs the examination. An entire examination may take from 20 min to 1.5 h, depending on the type and amount of information required. The design of the MR system restricts the subjects to a horizontal lying position inside the bore of the magnet. This means that tissue deformation, relevant to pressure ulcer research, can be examined only in a lying position, not under realistic conditions in a sitting position, such as when a patient is confined to a wheelchair.

MR has no known negative effects on living tissue, but some potential hazards, related to metal objects entering the scan room, should be considered. Because of possible interference with the high magnetic and RF fields present, patients who have a heart pacemaker, surgical staples, aneurysm clips, or any other implanted metal device are not allowed to undergo a MR scan.

The MR examinations of animals are similar to those of humans, except that the animals are usually sedated to avoid movement during the scans. This also allows for longer scanning times, up to several hours. MR examinations on small laboratory animals are usually performed with specialized high-field animal scanners.

Basic Contrast

The proton density, and the T_1 and T_2 relaxation times provide the basic contrast in MR images. The proton density is the distribution of water in tissue, which gives the main anatomical contrast in the images. The brightness of pixels in the MR images also depends, however, on the chemical and physical environment of the protons, which can be described by T_1 and T_2. The spin-lattice or longitudinal relaxation time T_1 describes the exponential increase of the spin magnetization towards equilibrium when placed in a strong magnetic field or when disturbed by a radio-frequency pulse. The spin-spin or transverse relaxation time T_2 describes the exponential decrease of the spin magnetization in the transverse plane (perpendicular to the static magnetic field). This transverse magnetization, which is created by tipping the spin magnetization from longitudinal equilibrium by a radio-frequency pulse, creates the measured signal in MRI.

The intensity of the MR signal is given in first approximation by

$$I \propto N e^{-TE/T_2}(1 - e^{-TR/T_1}) \tag{1}$$

where N, T_1, and T_2 are the proton density, the spin-lattice relaxation time and the spin-spin relaxation time, respectively. TR is the radio-frequency pulse repetition time and TE is the echo time, or signal delay time. Contrast is obtained because different tissues have different proton densities and relaxation times [22–25]. Equation 1 shows that when TR is long and TE is short compared to T_1 and T_2, respectively, the contrast is mainly determined by the proton density, yielding a so-called proton density-weighted image. When TR is of the order of the spin-lattice relaxation time, contrast is ob-

tained on the basis of differences in T_1, in which case the image is called a T_1-weighted image. When TE is of the order of the spin-spin relaxation time, contrast is obtained on the basis of differences in T_2, resulting in a so-called T_2-weighted image. Note that Eq. 1 holds only for a spin-echo imaging pulse sequence. For other imaging pulse sequences the intensity depends in a more complicated manner on N, T_1, and T_2 [20].

The spin-lattice relaxation time T_1 depends on the motion of water molecules in tissue and the interactions with surrounding macromolecules. The spin-spin relaxation time T_2 is in addition strongly affected by the slowly varying magnetic fields at the molecular level. A detailed discussion of the physical and chemical origin of the relaxation processes in living tissue is beyond the scope of this chapter. It is more useful to consider the relaxation times typically observed in musculoskeletal tissues and the effects of pressure ulcer pathology on these relaxation times. Table 18.1 shows typical relaxation times at 1.5 T for some relevant tissues.

The relevant pathologic conditions of pressure ulcers that affect muscle proton density and relaxation times are inflammation, haemorrhage, mass lesions, fibrosis, and fatty infiltration [1, 7]. Inflammation, oedema and haemorrhage usually lead to an increased proton density, caused by increased intracellular and extracellular free water. The T_1 and T_2 are increased because free water has longer relaxation times. Most mass lesions, such as solid neoplasms, abscesses and tumours, also are characterized by relaxation times that are prolonged relative to the surrounding tissues. Because both inflammatory processes and mass lesions lead to increased relaxation times, differentiation on the basis of relaxation times only is difficult. However, usually a clear distinction between the two can be made on the basis of morphology. Fibrous tissue formed by fibrosis does not provide much MR signal, due to low water content, and may be difficult to detect until a substantial amount of tissue has formed. Fat is characterized by a short T_1, and T_1-weighted MRI can therefore easily detect fatty infiltration.

Because of the well-documented effects of muscle pathology on the proton density and the relaxation times, contrast in proton density-weighted, T_1-weighted and T_2-weighted MRI provides a useful tool for the detection and diagnosis of pressure ulcers [8–11, 16]. This is illustrated in Fig. 18.1, showing transverse T_2-weighted MR images of the hind limbs of three rats

Table 18.1. Typical relaxation times for relevant human tissues at 1.5 T [22–25]

Tissue	T_1 (ms)	T_2 (ms)
Muscle	1077	47
Adipose tissue	260	84
Nerve	740	77
Bone marrow	250	25

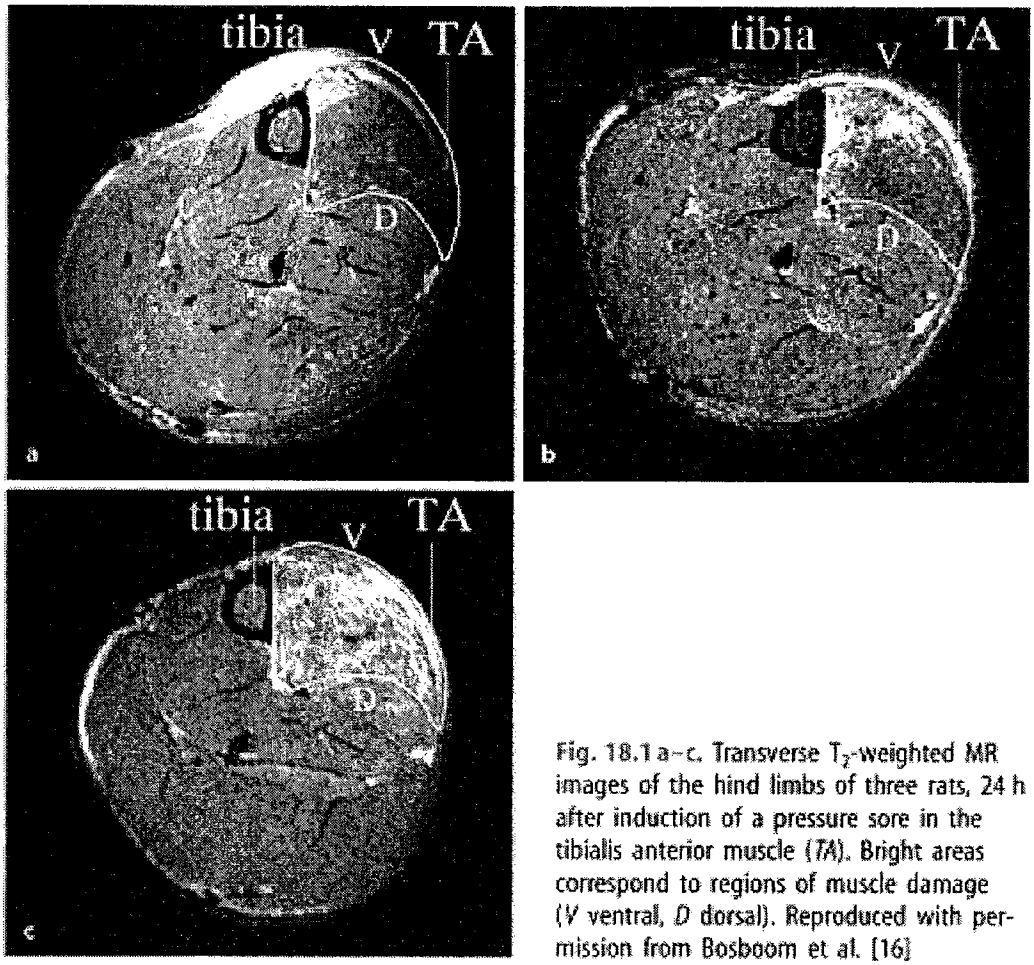

Fig. 18.1 a–c. Transverse T_2-weighted MR images of the hind limbs of three rats, 24 h after induction of a pressure sore in the tibialis anterior muscle (*TA*). Bright areas correspond to regions of muscle damage (*V* ventral, *D* dorsal). Reproduced with permission from Bosboom et al. [16]

24 h after induction of a pressure ulcer in the tibialis anterior muscle by compression [16]. Patchy regions with high signal intensity are observed in the muscle, probably caused by oedema due to inflammation. The amount of muscle damage assessed in vivo with MRI correlated well with the area of damage obtained from ex vivo histology.

Dynamic Deformation

In a number of recent studies it has been hypothesized that prolonged deformation of cells plays a major role in the onset of tissue damage [16, 26–31]. This hypothesis was tested on cultured cells [28, 31] and in a rat model in which the tibialis anterior muscle and overlying skin were compressed between an indenter and the tibia [16, 29, 30]. For the rat model, the amount and location of the pressure ulcers that developed were determined with histology and MRI (see Fig. 18.1), and the results were compared to finite-element calculations of shear strain distributions in the muscle during loading. Unfortunately, most calculations resulted in shear strain distri-